REMARKS

Support for the amendments to Claim 9 can be found as follows:

(A) "more than 13 weeks"

The minimum "13 weeks" in the expression "more than 13 weeks is supported at page 28, lines 10-16 of the Substitute Specification filed November 16, 2001.

Further, support for 100% engraftment "more than" 13 weeks can be found in Figure 2 of the present application which shows 100% engraftment is achieved for at least 21 weeks in Group I (6.5 Gy), and for at least 36 weeks for Group II (7.0 Gy), both of which represent the present invention.

(B) "reducing graft rejection"

Support for the expression "reducing graft rejection" can be found, *inter alia*, in Test Example 4 at page 23, line 28 to page 28, line 24 of the Substitute Specification.

(C) "said graft donor is a different animal of the same species of said recipient"

Support for the expression "said graft donor is a different animal of the same species of said recipient" can be found, *inter alia*, in Test Example 4, at page 26, line 17-20 of the Substitute Specification, wherein (BALB/cxDBA2) F1 mice (H-2K^d) (aged 7~8 weeks, 19~20 g, Japan SLC) are used as donor mice and B6 mice (H-2Kb) (aged 10~13 weeks, 20~23 g, Japan SLC) are used as the recipient mice.

Hence, the amendment to Claim 9 do not constitute new matter, and thus entry is requested.

On page 2 of the Office Action, the Examiner mintains the rejection of Claims 9-10 under 35 U.S.C. § 103 as being unpatentable over Slavin et al in view of Ildstat et al, Zhang et al and Sachs.

For the following reason, Applicants respectfully traverse the Examiner's rejection.

Only Ildstad et al teaches using TBI within the range claimed, i.e., at least 6.5 Gy. However, Ildstad et al can only be combined with the other cited references in hindsight, since Ildstad et al relates to mixed allogenic chimera.

Specifically, Figure 1 of Ilstadt et al shows that only about 80% on the recipients BMC are removed after 6.5 Gy.

Ildstad et al states, at col. 16, lines 55 *et seq*, that under these conditions, i.e., where the recipient was not fully cytoablated prior to allogeneic bone marrow transplantation, there is re-emergence of autologous stem cells within an environment of newly engrafted allogeneic bone marrow cells. Therefore, mixed allogeneic chimerism resulted even though only allogeneic bone marrow was infused as donor.

When donor BMC are administered iv (as taught in Ilstadt et al) there is reemergence of autologous (recipient) BMC (see column 16, lines 55 et seq), the donor BMC decrease over time and the donor organ is rejected over time (see Group III of Fig. 2 of the present specification).

In contrast, when using portal vein injection, after 6.5 Gy the residual recipient BMC decrease and the administered donor

BMC increase over time, i.e., fully allogeneic chimerism is achieved over time, and thus the donor cells and graft are not rejected (Fig. 2, Group I).

Hence, rejection of the donors cells and organ is reduced by combining portal vein injection of donor BMC (not recipient BMC) with at least 6.5 Gy of TBI. Thus, the present invention relates to achieving fully allogeneic chimerism.

While Ildstad et al may teach that allogeneic engraftment was reliably achieved in 100% of all animals conditioned with 7Gy, this relates to engraftment of donor BMC, not to engraftment of the transplanted organ.

As discussed in the Declaration of record, a 100% engraftment rate for BMC does not lead to 100% organ engraftment (see Figure 7 of Ildstad et al).

More specifically, Ildstad et al shows in Section 6.2.9 skin engraftment. In Figure 7 of Ildstad et al, data on B10 is provided, wherein 100% engraftment was achieved beyond day 19. However, this refers to engraftment of skin from the recipient, not donor skin. When looking at donor skin, Figure 7 shows that survival is decreased to about 90% after 19 days, i.e., grafts are rejected prior to week 13.

During a telephonic interview with the Examiner on September 14, 2006, the Examiner advised that the present specification and claims do not require that the donor graft organ be from a different animal than the recipient, i.e., it is the Examiner's position that claims are broad enough that the donor graft organ (e.g., skin) can be from a different location on the same animal, and in that case there would not be mixed

chimerism, i.e., such would encompass the B10 data in Figure 7 of Ildstad et al, where 100% engraftment is seen beyond day 19.

Applicants respectfully submit that this is a new and unjustified interpretation of the claims. However, to clearly distinguish the present invention from Figure 7 of Ildstad et al, Applicants hereby amend the claims to recite that the "donor is a different animal of the same species as the recipient."

During the above-noted telephonic interview with the Examiner, it was pointed out that in Figures 5, 7 and 20 of Slavin et al the BMC, spleen cells and the like are not "organ" grafts, and that 100% of BM stromographs in Example 14 again is not an "organ" graft, as claimed in the present application.

As to Tables 1-3 of Slavin et al, which relate to skin grafts, the Examiner was advised that these Tables only teach that 100% engraftment was achieved with TLI, and not with TBI.

Further, it was advised that Slavin et al teaches that TLI is preferred over TBI, and Figure 2 thereof shows that high doses of TLI resulted in decreasing the survival rate of the grafts, and thus teaches away from increasing the dose of TBI, as claimed in the present application.

Applicant further noted during the telephonic interview that in the examples of the present application, non T cell depleted BMC were used. When non T cell depleted BMC were used in Tables 2-3 of Slavin, the results show the non T cell depleted BMC actually induced graft versus host disease.

With respect to the present invention, as taught in paragraph 99 of the present specification:

> The results of this test example indicate that the immunotolerance inducing procedure comprising administration of the first pharmaceutical composition into the portal vein and the organ transplantation can be concurrently carried out. Therefore, in humans, too, the portal administration of the first pharmaceutical composition (bone marrow and other cells) from the donor and the organ transplantation can be concurrently performed. This technique is considered to be an epochal one in that the graft vs. host reaction (GvH reaction) can be prevented even without removal of T cells from the marrow cell fraction and the immunotolerance can be sufficiently maintained using only two doses of an immunosuppressant. TEST EXAMPLE 4

As taught in paragraph 122 of the present specification:

> The engraftment rate was slightly higher in the 6.5 Gy plus portal administration group. It appears that because the donor's hematopoietic stem cells are trapped in the recipient's liver with higher efficiency in this group, the rejection by radio-resistant immunocompetent cells in the recipient mice is more effectively avoided.

Slavin et al gives 4.0 Gy of TBI as an example of such a radiation dose (column 23, line 40, and column 34, line 58).

Therefore, a person skilled in the art could not foresee from the disclosure of Slavin et al that high levels of irradiation, in particular, high doses of TBI, would achieve better effects than those disclosed in Slavin et al.

In this regard, Ildstad et al discloses about 7.0 Gy of TBI. That is, Ildstad et al discloses a high dose level for TBI, which is not preferable according to Slavin et al.

Thus, a person skilled in the art would not have been motivated to combine Slavin et al's technique with Ildstad et al's technique. Even if these techniques were combined, a person skilled in the art would expect that using a high dose level of TBI as taught in Ildstad et al in the method of Slavin et al would merely achieve a worse effect than that disclosed in Slavin et al.

Sachs et al discloses 4.0 Gy of TBI and describes TBI and bone marrow cell administration performed on the same day. The 4.0 Gy of TBI disclosed in Sachs et al is the same as disclosed in Slavin et al. Thus, a person skilled in the art combining Slavin et al's technique with Sach et al's technique would expect only the same level of effects as achieved by Slavin et al.

In fact, even 6.0 Gy of TBI does not achieve an engraftment rate of 100%, as described in Test Example 4 on page 28, lines 5-10 of the Substitute Specification. Thus combining Sachs et al's technique with Slavin et al's technique, TBI with a radiation dose of 4.0 Gy, cannot achieve the excellent effect of the present invention due to the insufficient level of radiation.

Zhang et al describes the effects of intravenous and portal venous administrations of bone marrow cells on prolonged graft survival. Fig. 4 of Zhang et al shows that bone marrow cells administered by portal venous injection are accumulated in the liver at higher levels than by intravenous injection, and thus indicates that portal venous administration might provide a

higher immunological tolerance-inducing effect than intravenous administration.

However, even if Slavin et al's technique was combined with Zhang et al's technique, a person skilled in the art could neither predict therefrom whether the excellent immunological tolerance-inducing effect as achieved by the present invention could be achieved, nor foresee how irradiation before portal venous administration could affect immunological tolerance-inducing effects, much less reduce graft rejection as claimed.

As is clear from the above, a person skilled in the art would not have been motivated to combine Slavin et al, Ildstad et al, Sach et al and Zhang et al to provide an excellent immunological tolerance-inducing effect, much less reduce graft rejection as claimed. Even if these techniques were combined, a person skilled in the art could not foresee therefrom that the excellent immunological tolerance-inducing effect as achieved by the present invention could be achieved.

Based on the teaching of Slavin et al, a person skilled in the art would rather expect that a combination of Slavin et al, Ildstad et al, Sach et al and Zhang et al would achieve a lower effect than that disclosed in Slavin et al.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Slavin et al alone or when combined with the teachings of Ildstad et al and Zhang et al, and Sachs et al and in any event, such a combination can only be made in hindsight, which is legally

improper. Thus, Applicants request withdrawal of the Examiner's rejection.

In paragraph 5, on page 6 of the Office Action, the Examiner rejects Claims 9-10 under 35 U.S.C. § 112, first paragraph as containing new matter.

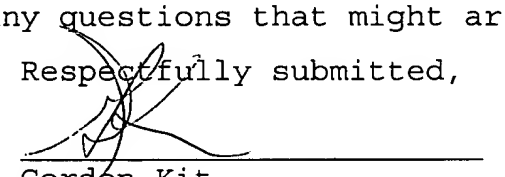
Specifically, the Examiner states that the expression "engraftment rate of 100% over a period of at least 13 weeks" is a departure from the specification and claims as originally filed, i.e., the specification merely shows an "engraftment rate of 100% up to week 13".

While Applicants respectfully submit that the specification, which includes the figures, clearly support "at least 13 weeks", in view of the amendments to Claim 9, this rejection has been rendered moot.

In view of the amendments to the claims and arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the telephone number listed below on any questions that might arise.

Respectfully submitted,



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